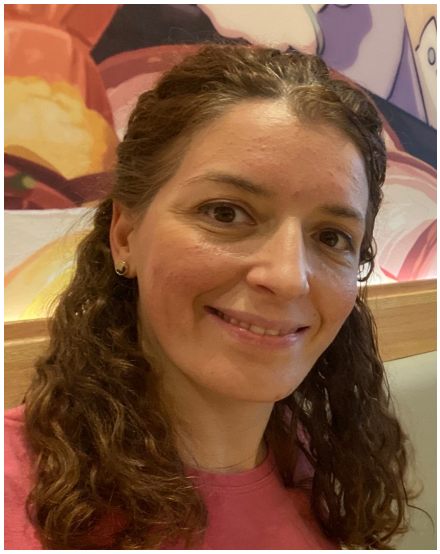
ACS Local Section
New York
Long Island Subsection

Optimizing the Metabolic Stability of Phosphodiesterase 5 Inhibitors



Dr. Jole Fiorito
Assistant Professor
Department of Biological and Chemical Sciences
New York Institute of Technology

Thursday, March 7, 2024
6:45 PM via Zoom
(Registration required prior to event)
Click here to register

Abstract: Phosphodiesterase 5 (PDE5) is a cyclic guanosine monophosphate-degrading enzyme involved in numerous biological pathways. Inhibitors of PDE5 are important therapeutics for the treatment of neurodegenerative diseases, including Alzheimer's disease (AD). We previously reported the first generation of quinoline-based PDE5 inhibitors for the treatment of AD. However, the short *in vitro* microsomal stability rendered them unsuitable drug candidates. Here we report a series of new quinoline-based PDE5 inhibitors. Among them, compound **4b**, 8-cyclopropyl-3-(hydroxymethyl)-4-(((6-methoxypyridin-3-yl)methyl)amino)quinoline-6- carbonitrile, shows a PDE5 IC_{50} of 20 nM and improved *in vitro* microsomal stability ($t_{1/2}$ = 44.6 min) as well as excellent efficacy in restoring long-term potentiation, a type of synaptic plasticity to underlie memory formation, in electrophysiology experiments with a mouse model of AD. These results provide an insight into the development of a new class of PDE5 inhibitors for the treatment of AD.

Biography: Dr. Jole Fiorito earned a Master of Science in Pharmaceutical Chemistry and her Ph.D. in Pharmaceutical Sciences from the University of Catania, Italy.
Following graduate school, she became a post-doctoral researcher at Columbia University in the TAUB Institute for Research on Alzheimer's Disease and the Aging Brain (Dr. Arancio Lab) and the Organic Chemistry Collaborative Center (Dr. Landry Lab). While at Columbia, she developed novel compounds that inhibit phosphodiesterase 5 (PDE5) enzymes and increase the phosphorylation of the transcriptional factor CREB through the nitric oxide signaling pathway, which is found to be impaired in Alzheimer's disease. These technologies are patent pending and have already generated interest from the pharmaceutical industry.
Currently, Dr. Fiorito's research interests are in developing multi-target small molecules against both HAT and PDE5 enzymes that are involved in several multifactorial diseases such as Alzheimer's disease and cancer. Dr. Fiorito has received an NIH Research Enhancement Award (R15) to conduct this research. She hopes her research will lead to novel disease-modifying therapeutics that can address unmet clinical needs.

Presented by the Long Island Subsection of the American Chemical Society